

Europe approximated fraction of HPV-driven oropharyngeal cancers is 25%, and laryngeal cancers only 5%, versus 50% and 35% suggested by HPV DNA studies for these anatomical sites, respectively. The use/usefulness of specific markers and marker combinations to define an HPV-driven tumor will be discussed.

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Role of HPV status on Radiotherapy outcome in the various tumour entities.

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The recent understanding of mechanisms of HPV-induced carcinogenesis has lead to the development of prophylactic vaccines, however radiotherapy still remains a major therapy in HPV-related cancer and despite concurrent chemotherapy, the outcome remains suboptimal. Therefore, improving the radiotherapeutic index remains an important challenge as well as defining predictive assays for treatment outcome of HPV-related tumours. Elucidating the influence of the HPV virus on tumour radiosensitivity is of major interest. There is several lines of evidence showing that head and neck HPV-positive tumours have better outcome compared to non HPV related tumours and given the role of HPV oncoproteins on tumor immunity, it is possible that the feature of immune and microenvironmental factors during radiation response could be specific to HPV related tumors. Genetic feature of HPV+ cervical cancer has also been investigated and 3q gain has been shown to be particularly frequent in cervical cancers infected with the HPV16 virus type (84%) as well as in oropharyngeal and lung cancers. Other cancers such as anal and penile cancers are caused by or at least are associated with HPV infection. HPV-associated malignancies have common molecular feature, however specific response can also be expected and interfere with response to radiotherapy such as the contribution of organ-specific microbiota. In any case, investigating radiation response in this various type of cancer would help to decipher the role of HPV in radiation sensitivity and assess whether HPV+ cancer cells are intrinsically more sensitive to radiotherapy; or if HPV+ tumors release upon radiotherapy immunogenic viral proteins that promote tumor clearance and may prevent recurrence. This difference may allow for different combination of treatment strategies to be developed.

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Clinical data (H&N, cervix, vulva, anal)

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Approximately 5% of all cancers worldwide are considered attributable to Human papillomavirus (HPV) and as such HPV associated cancers constitute a significant global disease burden. A causal relationship between HPV and cervical cancer was established almost 40 years ago and HPV is necessary for the development of cervical cancers, of which more than 99% harbour virus. Detection rates of HPV at other ano-genital sites (vulva, vagina and anus) are somewhat lower (65-80%), and clinical data suggest that outcome at these sites differ significantly dependent on the HPV-status of the tumors, in a way that patients with HPV-positive tumors have better prognosis compared to HPV-negative patients.

In head and neck cancer (HNSCC), tobacco and alcohol were until recently considered to be the major risk factors for

carcinogenesis. However, the putative role of HPV in HNSCC has been investigated since the 1980s, and at present sufficient molecular and pathological evidence exists to etiologically link HPV to a subset of HNSCCs. The strongest association with HPV is found in oropharynx cancer (OPC) where tumors of the tonsils are particularly associated with HPV infection, but high-risk HPV, predominantly HPV-16, has been found in HNSCC from all sites although with a significantly higher prevalence in OPC compared to tumors arising outside the oropharyngeal region (non-OPC). Numerous clinical studies have demonstrated a highly significant impact of tumour HPV/p16-status on radiotherapy (RT) outcome in advanced OPC where the influence of tumor HPV/p16-status seems indisputable. These observations are believed to be caused in part by a higher sensitivity of HPV/p16-positive tumors to RT, combined with a different and more favourable risk factor profile (including less heavy tobacco history) and better general health status in the group of patients with HPV/p16-positive disease. Less is known about the influence of HPV/p16-status in non-OPC and clinical data published so far have reached different conclusions. Data based on a rather large cohort of patients with advanced larynx and hypopharynx cancer treated with primary (chemo)radiotherapy suggested that the prognostic impact of HPV/p16-status does not extend to tumors of non-oropharyngeal origin. The reasons for this apparent site-specific difference in the prognostic impact of HPV/p16-status in HNSCC remain unsolved and warrant further investigation.

Presently there is substantial variation in the treatment strategies considered for patients with head and neck cancer dependent of the HPV/p16-status of the tumors. Some clinical trials are investigating whether de-intensified treatment strategies could result in avoidance of excessive toxicity without compromising outcome for selected patients with "low-risk" HPV/p16-positive OPC. At the opposite end of the spectrum other trials are investigating whether additional intensification of treatment could be beneficial for patients with HPV/p16-negative HNSCC based on their observed poor outcome, in order to secure optimal and safe treatment for these patients also.

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Estimation of HPV 16 and 18 subtypes, viral load and correlation with response to radio (chemo) therapy in cervical cancers

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Purpose/Objective: Etiologic role of Human Papilloma Virus (HPV) in cervical cancer is well established. Radio (chemo) therapy remains the mainstay of treatment. Response, relapses & overall outcome and correlation with HPV is not well known. With an aim to study this we undertook this study.

Materials and Methods: After Institutional Ethical clearance and obtaining written informed consent patients were invited to participate in this prospective observational study. Patients who were treated with radio (chemo) therapy for cervical cancer underwent quantitative estimation of HPV 16 and 18 viral load pre treatment, at treatment completion, 2 and 5 months post treatment on cervical biopsies/ brushings using polymerase chain reaction (PCR). The viral load were compiled, evaluated and correlated with standard clinical response evaluation.